Approval Date: APR 2 ....

FREEDOM OF INFORMATION SUMMARY

Supplemental NADA

141-199

Rimadyl® Injectable
(carprofen)

"...for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs."

PFIZER, INC.
235 East 42nd Street
New York, NY 10017

NADA 141-199 FOIS.

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FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION

a. File Number:	141-199
b. Sponsor:	Pfizer Inc 235 East 42nd St. New York, NY 10017 Drug Labeler Code: 000069
c. Established Name:	carprofen
d. Proprietary Name:	Rimadyl® Injectable
e. Dosage Form:	Injectable solution
f. How Supplied:	This product is available as a 50 mg/ml sterile solution in a 20 ml bottle.
g. How Dispensed:	Prescription (Rx)-U.S. Federal Law restricts this drug to use by or on the order of a licensed veterinarian.
h. Amount of Active Ingredient:	Each ml contains 50 mg of Rimadyl®.
i. Route of Administration:	subcutaneous injection
j. Species/Class:	dog
k. Recommended Dosage:	The recommended dosage for subcutaneous administration to dogs is 2 mg/lb (4.4 mg/kg) of body weight daily. The total dose may be administered as 2 mg/lb of body weight once daily or divided and administered as 1 mg/lb (2.2 mg/kg) twice daily. For the control of postoperative pain, administer approximately 2 hours before the procedure.
l. Pharmacological Category:	Non-steroidal, anti-inflammatory drug (NSAID)
m. Indications:	Rimadyl® Injectable is indicated for the relief of pain and inflammation associated with osteoarthritis, and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

n. Effect of Supplement: This supplement to NADA 141-199 provides revisions to 21CFR 522.312 (2) *Indications for Use.* To add a claim for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

2. EFFECTIVENESS:

Clinical effectiveness of the recommended Rimadyl® Injectable dosages of 1 mg/lb body weight twice daily and 2 mg/lb body weight once daily for the relief of pain and inflammation associated with osteoarthritis is contained in the original and supplemental Freedom of Information Summaries for NADA 141-199 dated March 3, 2003 and March 25, 2003.

a. Dosage Characterization:

Studies supplied in NADA 141-199 provide evidence of effectiveness for Rimadyl® Injectable for the relief of pain and inflammation associated with osteoarthritis. With support for effectiveness for the relief of pain and inflammation associated with osteoarthritis following administration of a single daily dose of Rimadyl® Injectable, a dose of 2 mg/lb once daily was selected for confirmation of effectiveness in the control of postoperative pain.

Clinical effectiveness of Rimadyl® Injectable at 2 mg/lb of body weight once daily for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs is demonstrated in three U.S. multicenter field studies involving a variety of surgical procedures. The intensity of surgical pain may vary with the procedure performed, the duration of the procedure, and the surgical technique used; therefore, the requirement for pain control may vary for different surgical procedures.

Surgical inductions included the use of combinations of tranquilizers, barbiturates, inhalant anesthetics, anticholinergics, antibiotics and parenteral fluids.

b. Substantial Evidence:

(1) Field Efficacy and Safety for the Relief of Postoperative Pain Associated with Ovariohysterectomies in Dogs (Study No. 1963C-60-99-360)

(a) Type of Study: Multicenter Field Study

(b) Investigators:

Name
Dr. Douglas C. Andrews Falmouth Veterinary Hospital Falmouth, ME 04105
Dr. John Bradley Bradley Animal Hospital Lawrence, KS 66046
Dr. R.Scott Buzhardt The Animal Center Zachary, LA 70791
Dr. Peter Davis Pine Tree Veterinary Hospital Augusta, ME 04330
Dr. Stuart Gluckman Mendon Village Animal Care Mendon, NY 14506
Dr. David Hancock Perinton Animal Hospital Victor, NY 14564
Dr. Stephen L. Jones Lakeside Animal Hospital Moncks Corner, SC 29416

Name
Dr. Sharon Lachette White Haven Veterinary Hospital White Haven, PA 18661
Dr. David K. Lukof Harleysville Veterinary Hospital Harleysville, PA 19438
Dr. Mark Marks Marks Veterinary Hospital Lawrence, KS 66047
Dr. Dean Rund Grant Avenue Pet Hospital Springfield, MO 65807
Dr. Susan B. Thompson Pet Vet Animal Hospital Mt. Pleasant, SC 29464
Dr. Paul Urband East Haddam Veterinary Clinic East Haddam, CT 06423

(c) General Design:

1 Purpose: The objective of the study was to evaluate the effectiveness and safety of Rimadyl® at a dose of 2 mg/lb (4.4 mg/kg) administered subcutaneously approximately 2 hours prior to surgery, and once daily thereafter for 2 days, as needed, for the control of postoperative pain associated with ovariohysterectomies in dogs.

2 Test Animals: One hundred and thirteen client-owned female dogs from 13 locations, ranging in age from 12 weeks to 10 years, entered the study. Dogs presenting in the course of clinical practice for an elective ovariohysterectomy were admitted to the study. A total of 59 dogs were treated with Rimadyl® and 54 dogs received placebo; these groups represented 73 purebred and 40 mixed-bred dogs.

3 Control Drug: 0.9% Sodium Chloride

4 Dosage Form: Injectable solution (proposed commercial formulation)

5 Route of Administration: Subcutaneous injection

6 Dosages Used: 2 mg/lb administered approximately 2 hours prior to surgery, then once daily thereafter for 2 days, as needed

7 Test Duration: 3 days

8 Parameters measured: Clinical assessment of pain was performed by the veterinarian prior to surgery (Day -1 or Day 0), approximately 4, 8, and 12 hours post-surgery, twice daily on Days 1 and 2, and once on Day 3. The procedure for assessing the animals' pain included observation of demeanor, attention and response, interest in food and water, movements in a confined space, and palpation of the surgical site. The degree of pain was quantified using a Visual Analog Scale (VAS).

Hematology, clinical chemistry, coagulation, urine, and fecal occult blood analyses were performed prior to treatment and upon study completion (Day 3). Approximately 24 hours post-surgery (Day 1), coagulation status was measured.

Effectiveness was based upon *a priori* contrasts among least squares means of VAS scores to assess the difference between placebo and Rimadyl® treatments. In addition, the number of animals withdrawn from the study due to lack of effectiveness was compared for each treatment.

Safety was evaluated by comparing the clinical pathology results from samples collected prior to surgery to the results from samples collected on Day 1 and Day 3. In addition, the abnormal health observations following treatment were summarized.

(d) Results: One hundred and eleven of the 113 dogs enrolled in the study were included in the complete effectiveness analysis. Two dogs were excluded from part of the analysis (1 placebo-treated and one Rimadyl®-treated animal) because the Test Article was administered prior to the Day 0 baseline assessment. Duration of treatment is summarized in Table 1. Rimadyl®-treated dogs required fewer additional treatments compared to dogs administered the placebo. Rimadyl®-treated dogs were significantly less painful 4, 8, and 12 hours post-surgery and on the first and second assessment on the first day after surgery ($P \leq 0.05$). Results of pain assessment using the VAS are provided in Table 2. Two placebo-treated dogs and no Rimadyl®-treated dogs were withdrawn due to lack of effectiveness.

Table 1. Duration of Treatment

Days of Test Article Administration	Number of Dogs Receiving Treatment		Overall
	Placebo	Rimadyl®	
Day 0	27	40	67
Days 0 and 1	11	8	19
Days 0 and 2	1	1	2
Days 0, 1, and 2	15	10	25
Total	54	59	113

Table 2. Analysis of Pain Assessment Using a Visual Analog Scale

Assessment	Visual Analog Scale Score (mm)				
	Placebo		Rimadyl®		*P*-values
	n[a]	LSM ± SEM[b]	n[a]	LSM ± SEM [b]	
Day 0					
preoperative	53	-1.40 ± 3.01	58	-1.29 ± 2.97	0.9656
1st postoperative	54	23.46 ± 3.01	59	15.57 ± 2.97	0.0025
2nd postoperative	52	22.00 ± 3.02	59	16.08 ± 2.97	0.0212
3rd postoperative	52	21.09 ± 3.02	59	15.63 ± 2.97	0.0323
Day 1					
1st assessment	52	19.52 ± 3.02	59	13.32 ± 2.97	0.0161
2nd assessment	52	16.50 ± 3.02	59	9.86 ± 2.97	0.0103
Day 2					
1st assessment	52	11.09 ± 3.02	59	8.03 ± 2.97	0.2215
2nd assessment	52	8.75 ± 3.02	59	6.71 ± 2.97	0.4134
Day 3					
only assessment	52	6.56 ± 3.02	59	5.17 ± 2.97	0.5766

[a] Not all animals had every pain assessment completed, therefore, the sum of animals listed under Day 0 to Day 3 may not equal the number of treated animals.
[b] Least Squares Means ± Standard Error of the Mean

(e) Statistical Analysis: *A priori* contrasts among least squares means of the VAS scores using a repeated measures model were used to assess the difference between placebo and Rimadyl® treatments at each time point. The analyses were performed using SAS 6.12 (Statistical Analysis System). Statistical difference was assessed at the 5% level of significance ($P \leq 0.05$).

(f) Conclusions: Under clinical conditions, Rimadyl® administered subcutaneously at 2 mg/lb (4.4. mg/kg), approximately two hours prior to surgery and once daily thereafter, as needed for two days, is safe and effective in controlling postoperative pain associated with ovariohysterectomies in dogs.

(g) Adverse Reactions: Clinical pathology data indicated that Rimadyl® was well tolerated. Changes in clinical pathology variables were similar in dogs administered Rimadyl® compared with placebo cases. All mean pre- and post-treatment laboratory results were within the laboratory reference range with the exception of the Day 1 fibrinogen in both treatments. Two Rimadyl®-treated dogs had a greater than two-fold increase in alkaline phosphatase pre-surgery to Day 3. There were no placebo-treated dogs with a two-fold increase that resulted in values outside the reference range. Two Rimadyl®- and 1 placebo-treated dog had a greater than two-fold increase in AST. Nine Rimadyl® and six placebo cases went from normal baseline to elevated Day 3 WBCs (white blood cell counts). Ketonuria was common in both Rimadyl® and placebo-treated cases. None of the animals showed clinical signs associated with these laboratory changes. There were no serious adverse drug experiences or mortalities related to Rimadyl®. Similar types and numbers of abnormal health observations were reported between placebo- and Rimadyl®-treated dogs and are summarized in Table 3.

Table 3. Abnormal Health Observations reported during the field study (number of dogs = 113)

Abnormal Health	**Rimadyl® (% of dogs)**	**Placebo (% of dogs)**
Vomiting	23.7	27.8
Diarrhea[a]	3.4	9.3
Aural (ear) Disease	1.7	0
Conjunctivitis	1.7	0
Dehiscence	1.7	0
Seroma	1.7	0
Skin Lesion, self inflicted	1.7	0
Lethargy	0	1.9

[a] Includes soft stool, fecal incontinence

(2) Field Efficacy and Safety for the Relief of Postoperative Pain Associated with Cruciate Injuries in Dogs (Study No. 1963C-60-99-361)

(a) Type of Study: Multicenter Field Study

(b) Investigators:

Name	Name
Dr. James F. Biggart Veterinary Surgery Service, Inc. Berkeley, CA 94710	Dr. Paul E. Howard Vermont Veterinary Surgery Colchester, VT
Dr. R.Scott Buzhardt The Animal Center Zachary, LA 70791	Dr. Stephen L. Jones Lakeside Animal Hospital Moncks Corner, SC 29416
Dr. Peter Davis Pine Tree Veterinary Hospital Augusta, ME 04330	Dr. Stephen Ladd Hillsboro Animal Hospital Nashville, TN 37215
Dr. James M. Fingeroth Vet Specialists of Rochester Rochester, NY 14623	Dr. Steven A. Martinez Washington State University Pullman, WA 99164
Dr. Richard Gallina Germantown Animal Hospital Germantown, TN 38138	Dr. Roger L. Sifferman Bradford Park Vet Hospital Springfield, MO 65804

(c) General Design:

1 Purpose: The objective of the study was to evaluate the effectiveness and safety of Rimadyl® at a dose of 2 mg/lb (4.4 mg/kg) administered subcutaneously approximately 2 hours prior to surgery, and once daily thereafter for 3 days, as needed, for the control of postoperative pain associated with surgical repair of cruciate injuries in dogs.

2 Test Animals: Ninety-eight client-owned dogs (58 females and 40 males) from 10 locations, ranging in age from 1 to 12 years, entered the study. Dogs presenting in the course of clinical practice for surgical repair of a cruciate injury were admitted to the study. A total of 48 dogs were treated with Rimadyl® (48 were evaluated for safety and 47 were evaluated for effectiveness) and 50 dogs received placebo; these groups represented 60 purebred and 38 mixed-bred dogs. Surgical procedures included joint stabilization and/or arthrotomy (fabellar suture, imbrication, fibular head transposition and autograft), trochleoplasty, and tibial plateau leveling osteotomy.

3 Control Drug: 0.9% Sodium Chloride

4 Dosage Form: Injectable solution (proposed commercial formulation)

5 Route of Administration: Subcutaneous injection

6 Dosages Used: 2 mg/lb administered approximately 2 hours prior to surgery, then once daily thereafter for 3 days, as needed

7 Test Duration: 4 days

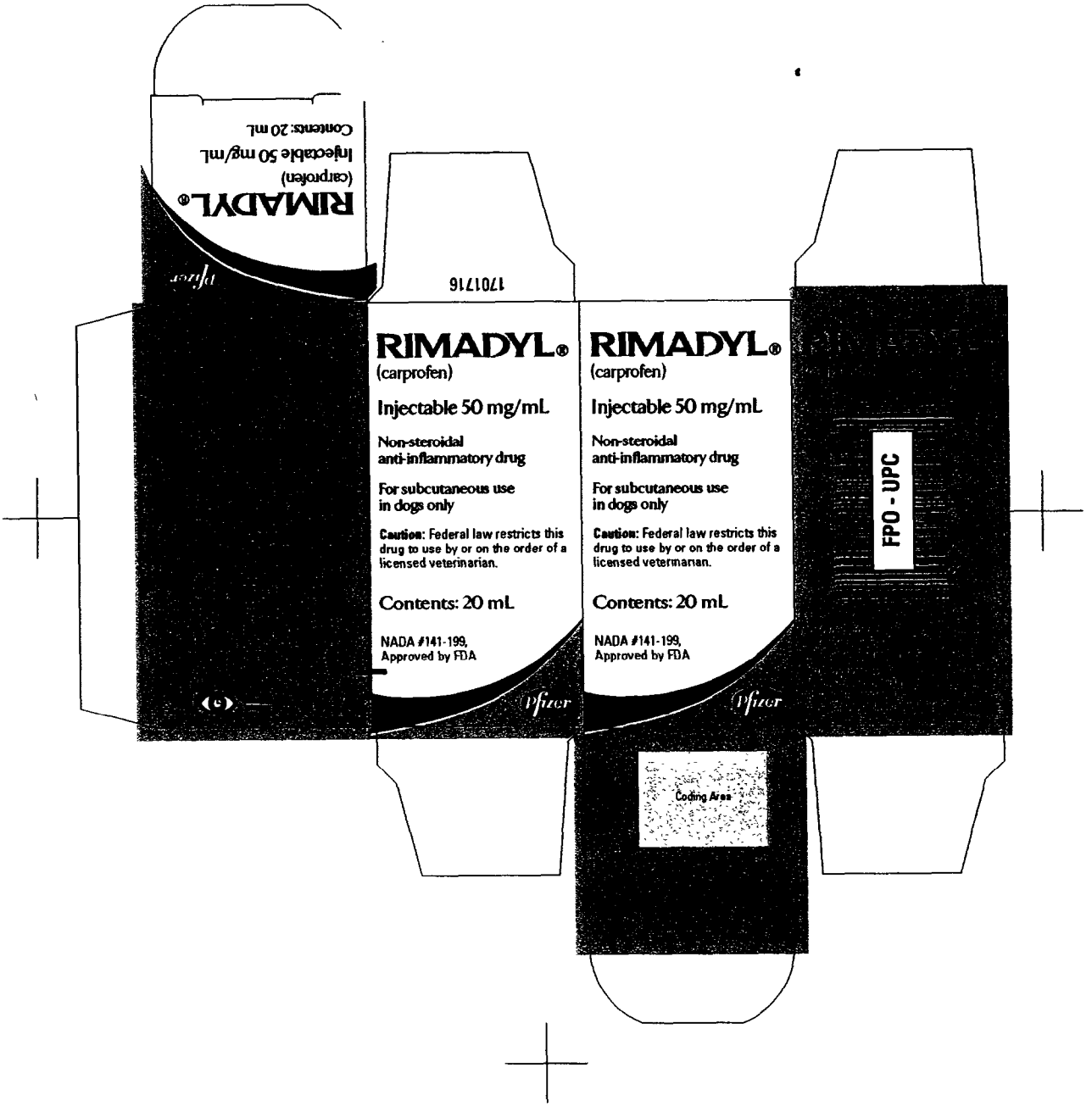
8 Parameters measured: Clinical assessment of pain was performed by the veterinarian prior to surgery (Day -1 or Day 0), approximately 4, 8, and 12 hours post-surgery, twice daily on Days 1, 2, 3, and once on Day 4. The procedure for assessing the animals' pain included observation of demeanor, attention and response, interest in food and water, movements in a confined space, palpation of the surgical site, and flexing and extending the affected joint. The degree of pain was quantified using a Visual Analog Scale (VAS).

Hematology, clinical chemistry, coagulation, urine and fecal occult blood analyses were performed prior to treatment, and upon study completion (Day 4). Approximately 24 hours post-surgery (Day 1), coagulation status was measured.

Effectiveness was based upon *a priori* contrasts among least squares means of VAS scores to assess the difference between placebo and Rimadyl® treatments. In addition, the number of animals withdrawn from the study due to lack of effectiveness was compared for each treatment.

Safety was evaluated by comparing the clinical pathology results from samples collected prior to surgery to the results from samples collected on Day 1 and Day 4. In addition, the abnormal health observations following treatment were summarized.

(d) Results: Ninety-seven of the 98 dogs enrolled in the study were included in the effectiveness analysis. Of the 98 total, one dog was excluded from part of the effectiveness analysis and one dog was excluded from the entire effectiveness analysis due to protocol deviations or failure to meet the enrollment criteria. Duration of treatment is summarized in Table 4. Rimadyl®-treated dogs were significantly less painful 4, 8, and 12 hours post-surgery ($P \leq 0.05$) and on the remaining assessments on Days 1, 2, 3, and 4 after surgery ($P \leq 0.05$). Results of pain assessment using VAS are provided in Table 5. Nine placebo-treated dogs and five Rimadyl®-treated dogs were withdrawn due to lack of effectiveness.


RIMADYL®
(carprofen)
Injectable 50 mg/mL
Contents: 20 mL
Pfizer
1701716
RIMADYL®
(carprofen)
Injectable 50 mg/mL
Non-steroidal
anti-inflammatory drug
For subcutaneous use
in dogs only
Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
Contents: 20 mL
NADA #141-199,
Approved by FDA
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NADA #141-199,
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Pfizer
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Contents: 20 mL

NADA #141-199,
Approved by FDA

Pfizer

Each mL of Rimadyl Injectable contains 50 mg of carprofen

Indications: Rimadyl is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

Dosage: For complete product information, see package insert.

Warnings: Keep out of reach of children. Not for human use. Consult a physician in cases of accidental human exposure.

For use in dogs only. Do not use in cats.

Please Refer to Insert for Complete Warnings and Precautions

Store under refrigeration at 2°–8°C (36°–46°F).

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